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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/688,028	10/17/2003	Abraham Dijke	33449-8004.US00	2188

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EXAMINER	
SODERQUIST, ARLEN	
ART UNIT	**PAPER NUMBER**
1797	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/688,028	DIJKE, ABRAHAM
	Examiner	Art Unit
	Arlen Soderquist	1797

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

2. Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cejpek or Burdaspal (Alimentaria 2001, 38, 117-126, hereinafter referred to as Burdaspal '01 or Alimentaria 2003, 40, 3-14, hereinafter referred to as Burdaspal '03, both newly cited and applied) in view of Williams and Krishen.

In the paper Cejpek presents a simplified extraction and cleanup procedure for the determination of PAHs in fatty and protein-rich matrixes. A simplified analysis procedure for the determination of 12 priority polycyclic aromatic hydrocarbons (phenanthrene, anthracene, fluoranthene, pyrene, benz(a)anthracene, chrysene, benzo(b)fluoranthene, benzo(k)fluoranthene, ***benzo(a)pyrene*** (BaP), dibenz(a,h)anthracene, benzo(ghi)perylene and indeno(1,2,3-cd)pyrene) in meat products and other biological materials has been developed. As a first step, ultrasonic extraction with chloroform (a PAH soluble solvent) for isolation of analytes was used. This is procedure C on page 68. Gel permeation chromatography on Bio-Beads S-X3 utilizing chloroform as mobile phase was applied to remove interferences (lipids, pigments etc.). The paragraph bridging pages 72 and 75 discusses the gel permeation step including the use of THF as mobile phase by prior investigators. The paragraph that follows on page 75 discusses the recovery and recognizes that recovery of the more volatile PAH compounds occurs during an evaporation step. HPLC with fluorescence detection was employed for quantitation of analytes. Table 3 shows the variation of the excitation wavelengths for the different compounds. Page 69

teaches that water/acetonitrile mixtures were used in the HPLC determination process. Recoveries at a μg/kg (ppb level) spiking level ranged from 53% (phenanthrene) to 112% (benzo(k)fluoranthrene) with relative standard deviations in the range of 15% (benzo(k)fluoranthene) to 49% (anthracene). Table 7 shows that the recovery of BaP was at least 99%. Figure 5a shows detection of 0.2 μg/kg (0.2 ppb). The first sentence of page 66 recognizes that the prior art methods are time consuming and cumbersome. The last paragraph of page 78 teaches that the time shortening of procedure C reduces the risk of PAH loss with the main loss attributed to the solvent removing step. Cejpek does not teach the interfacing of the gel permeation chromatography with the HPLC determination apparatus or the use of tetrahydrofuran as the solvent in the gel permeation chromatography process.

In the paper Burdaspal '01 describes an appropriate method for determination of polycyclic aromatic hydrocarbons in pomace olive oil by gel permeation chromatography and high performance liquid chromatography. This analytical method determines the content of polycyclic aromatic hydrocarbons in pomace olive oil samples by high performance liquid chromatography with fluorescence detection including a previous step to purify the samples by gel permeation chromatography. This method is based and enlarges the scope of a procedure described recently for the specific determination of benzo(a)pyrene in native olive oil and pomace olive oil (Alimentaria, 327, 11-18, 2001). The method has been internally validated for the determination of the eight polycyclic aromatic hydrocarbons specified in the Orden of July 25, 2001, published in the Boletin Oficial del Estado (Spanish Official State Bulletin) ndegree 178 and referred to setting limits for certain polycyclic aromatic hydrocarbons in pomace olive oil: benzo(a)pyrene, benzo(e)pyrene, benzo(a)anthracene, benzo(b)fluoranthene, benzo(k)fluoranthene, dibenzo(a,h)anthracene, benzo(g,h,i)perylene and indeno(1,2,3 -c,d)pyrene. The limit of determination was 0.57 μg/kg (less than 1 ppb) for each hydrocarbon (see tables 1-8 on pages 122-123). Table 9 shows the recovery of the various PAH including over 99% for benzo(a)pyrene. The results of this validation study show the usefulness of this method as a tool to control the presence of those hydrocarbons. Burdaspal '01 does not teach the interfacing of the gel permeation chromatography with the HPLC determination apparatus or the use of tetrahydrofuran as the solvent in the gel permeation chromatography process.

In the paper Burdaspal '03 describes an appropriate analytical method to determine the contents of polycyclic aromatic hydrocarbons in samples of shellfish and fish by high performance liquid chromatography with fluorescence detection including a previous step to purify the crude extracts by gel permeation chromatography. This method is based and enlarges the scope of a procedure described formerly for the specific determination of polycyclic aromatic hydrocarbons in pomace olive oil (Alimentaria, 328, 117-126, 2001). The method has been internally validated for the determination of the eight polycyclic aromatic hydrocarbons specified in the Orden of July 25, 2001, published in the Spanish Official State Bulletin no. 178: benzo(a)pyrene, benzo(e)pyrene, benzo(a)anthracene, benzo(b)fluoranthene, benzo(k)fluoranthene, dibenzo(a,h)anthracene, benzo(g,h,i)perylene and indeno(1,2,3-c,d)pyrene, in fresh mussels and horse mackerel. The limit of determination was at least 0.5 μg/kg (less than 1 ppb) for each hydrocarbon (see tables 1-16 on pages 8-11). Burdaspal '01 does not teach the interfacing of the gel permeation chromatography with the HPLC determination apparatus or the use of tetrahydrofuran as the solvent in the gel permeation chromatography process.

In the paper Williams teaches interface development of a non-aqueous size-exclusion chromatography coupled on-line to reversed-phase high-performance liquid chromatography and applications to the analysis of low-molecular-weight contaminants and additives in foods. An interface has been developed which permits the on-line coupling of size-exclusion chromatography (SEC) in tetrahydrofuran with aqueous reversed-phase high-performance liquid chromatography. The interface isolates the required size exclusion chromatography fraction and dilutes it with water to ensure reconcentration of analytes on the reversed-phase column prior to gradient elution. Operational parameters and the influence of analyte polarity have been examined in detail. A predictive system is presented for determining the applicability of the system to any analyte, based on solute retention times on an ODS phase eluted with a methanol—water gradient. The method is illustrated with examples of direct analyses of crude lipid extracts from a snack product for 2,6-di-tert-4-methylphenol and from chocolate for dibutyl phthalate. Detection limits of ca. 0.5 mg/kg have been achieved. The paragraph bridging pages 316-317 teach that size-exclusion chromatography is closely related to gel permeation chromatography, gel permeation chromatography has been applied to lipid cleanup for pesticide

analysis and an automated system for this purpose was commercially available. This paragraph also teaches that reverse phase HPLC and size exclusion chromatography offer complimentary advantages. The first full paragraph of page 317 teaches that it is a simple matter to combine size exclusion chromatography with reversed phase HPLC using a column switching technique. The second full paragraph of page 317 discusses the online combination of the two columns. The experimental section on page 317 teaches that the size exclusion material is a poly(styrene-divinylbenzene) material. Page 319 under the system development heading teaches that the polystyrene is a preferred material for the size exclusion chromatography to separate lipophilic components from small molecules and that THF is one of a group of effective solvents that also includes toluene and chloroform. The last full paragraph of the page teaches that there is a need to use a solvent as the size exclusion chromatography eluent that is miscible with water. Of the group suitable solvents for the size exclusion chromatography, only THF is a practical candidate. The last full paragraph of page 323 teaches that any analyte of limited water solubility would be suitable for separation on the coupled system being described. The paragraph bridging pages 323-324 teaches a detection limit of at least 0.5 mg/kg and ways to improve the detection by changing things such as the SEC column length.

In the paper Krishen teaches gel permeation chromatography of low molecular weight materials with high efficiency columns. Improvements in the efficiency of small pore packing materials and column preparation have advanced the speed and convenience of gel permeation chromatography to that of gas chromatography and high speed liquid chromatography. Lack of volatility or the absence of significant differences in polarity, solubility, or ionic characteristics, do not pose problems in this technique. A single column, 610 mm × 8 mm, showed a theoretical plate count of 16,000. By using THF as the eluant at a flow rate of 0.5 mL/min, separations in the molecular weight range of 100-2000 were achieved in <30 minutes. A difference of 1 carbon atom was sufficient for satisfactory resolution of components on the lower molecular weight range. This technique was operated with a dual detection system, differential refractive index and UV absorption at 254 nm, to provide additional information. It was applied to low molecular weight entities encountered in the analysis of plasticizers, antioxidants, various condensation products, and other oligomeric species. Figure 4 shows the separation of epoxidized soy bean oil (triglycerides and fatty acids) from other components using

tetrahydrofuran as the eluting solvent. In the experimental section of page 898, the gel used is taught as a polystyrene-divinylbenzene gel.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to perform the method of Cejpek, Burdaspal '01 or Burdaspal '03 in a automated manner as taught by Williams because of the close relationship between size exclusion chromatography and gel permeation chromatography as taught by Williams, the similarity of the column packing material as shown by Williams and Krishen and the benefits of automation as taught by Williams (providing a way to transfer the solvent between columns without requiring a solvent removal/evaporation step which Cejpek clearly recognizes as the step in which most of the sample losses occur). It would have been obvious to one of ordinary skill in the art at the time the invention was made to use tetrahydrofuran as the elution solvent in the gel permeation separation step of Cejpek, Burdaspal '01 or Burdaspal '03 as taught by Krishen and Williams because of its ability to separate triglycerides from other types of molecules as shown by Krishen and Williams, its water miscibility as taught by Williams and the rapidity of that process as taught by Krishen.

3. Applicant's arguments filed August 27, 2007 have been fully considered but they are not persuasive. First it is noted that Burdaspal '01 and Burdaspal '03 are similar to Cejpek as a primary reference. Thus the comments which follow are appropriate for the combinations based on thus primary references as well. It is also noted that both of these references have been submitted for translation.

Relative to the argument that the combination of Cejpek and Williams is not proper because it would render the Cejpek process unsatisfactory or useless for its intended purpose, examiner notes that Williams also starts with an extraction step using a solvent mixture of acetone and hexane (paragraph bridging pages 317-318) which was replaced by toluene for loading onto the column. Williams clearly shows that the solvent in which the sample is dissolved for loading onto the first column does not need to be the same as that used as the mobile phase for the first separation. Additionally, Williams clearly considered chloroform and THF as possible solvents for use on the method and chose THF because of its miscibility with water which facilitates the loading of the sample on the HPLC column (page 319). Thus there is, in the teachings of Williams, that would have motivated one of ordinary skill in the art at the

time of the invention to use THF as the mobile phase in the GPC in order to combine it with the reversed phase HPLC. Examiner also points out that claim 1 does not exclude chloroform from the first eluting solvent nor does it require the eluting solvent and the solvent in which the PAH have low solubility are miscible with each other. Thus this argument is not commensurate in scope with the claims. Examiner also notes that if the number or choice of solvents is limited, then the language of the claims should be correspondingly limited to the one or two solvents that work.

Relative to the sub-ppb level of detection of PAH, examiner points out that claim 1 does not require more than the detection of a single PAH and does not require any particular detection level. Thus, thus argument is clearly not commensurate in scope with the instant claims. Even when a detection level for a PAH is required, it is only for benzo[a]pyrene. Thus other compounds can be detected at any level and still meet the claims. Furthermore, it is not clear what the detection level will be because Williams is not detecting PAH. However there is an expectation that the detection level would be lower than that reported by either of Cejpek or Williams based on the fact that the Williams method eliminates a step of solvent removal that Cejpek clearly teaches as the primary step in which PAH are lost. Also, Williams teaches that it is possible to improve the process by modifying the method in ways such as lengthening the first column. Thus, Williams also recognizes that the detection limit can be improved and suggests at least one method of causing the improvement to happen. Thus there would have been an expectation that the claimed detection limit of PAH would be reachable with the proposed combination. Again it is noted that if there are limitations to the process such as types of solvents or limitations on the column materials or sizes that are required to reach the sub-ppb detection level, those features are not now required by claim 1.

4. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The additionally cited art is directed to analysis of PAH and use of gel permeation chromatography.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arlen Soderquist whose telephone number is (571) 272-1265. The examiner can normally be reached on Monday-Thursday and Alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Arlen Soderquist

Arlen Soderquist
Primary Examiner
Art Unit 1797